DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103946/0

July 12, 2002

Sanofi-Synthelabo, Inc.
Attention: Mr. Mark Moyer
Director, Drug Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Mr. Moyer:

This letter hereby issues Department of Health and Human Services U.S. License No. 1294 to Sanofi-Synthelabo, Inc., Malvern, Pennsylvania in accordance with the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product Rasburicase. Rasburicase is indicated for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.

Under this authorization, you are approved to manufacture Rasburicase at your facility, Sanofi Recherche, in ——— Final formulated drug product will be manufactured, filled, labeled and packaged at Sanofi-Synthelabo, in ———. In accordance with approved labeling, your product will bear the proprietary name Elitek and will be marketed in 1.5 mg single-use vials.

The dating period for Rasburicase shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for drug substance shall be ——— when stored at —°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Rasburicase to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specification.

Any changes in the manufacturing, testing, packaging or labeling of Rasburicase or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 601.27). We note that you have fulfilled the pediatric study requirement at this time.

We acknowledge your written commitments as described in your letter of July 12, 2002, and as outlined below:

Chemistry Manufacturing and Controls:

1. To submit a complete validation report for the ——— method of determining urate oxidase enzyme activity, including a review of provisional acceptance criteria on the basis of additional data, by August 31, 2002. The provisional limits submitted to the BLA have been implemented for all production batches.

2. To submit a complete validation report for the revised ——————————— analysis used in drug substance release testing and for in-process testing, including a review of provisional acceptance criteria on the basis of additional data, by August 31, 2002. The provisional limits submitted to the BLA have been implemented for all production batches.

3. To submit a complete validation report for the revised ——————————— analysis used in drug substance release testing, including a review of provisional acceptance criteria on the basis of additional data, by August 31, 2002. The provisional limits submitted to the BLA have been implemented for all production batches.

Clinical:

4. To develop a quantitative ELISA for antibodies in patient sera for use in clinical safety studies and to submit information demonstrating assay sensitivity (with limit of quantification defined in mass units), specificity, reproducibility, robustness, and ruggedness. Until the final assay is validated, serum samples will be collected and banked for future analysis. The protocol for assay methods and the validation plan for the new ELISA will be submitted to CBER by August 31, 2002. The complete validation data will be available by March 31, 2003, and a final report submitted to CBER by September 30, 2003.

5. To submit information on the enzyme inhibition (antibody neutralization) assay to be used in clinical safety studies, demonstrating assay sensitivity, specificity,

reproducibility, robustness, and ruggedness. This information will include assessments of optimal concentrations of reagents to detect antibodies, and assurance that pharmacological levels of product in serum samples do not influence detection of antibodies. The protocol for assay methods and the validation plan for the new antibody neutralization assay will be submitted to CBER by December 30, 2002. The validation data will be available by June 30, 2003, and a final report submitted to CBER by September 30, 2003.

6. To design an appropriate antigen-specific assay for IgE assessment, such as RAST or radioallergosorbent testing, and to use the specific assay for IgE, in addition to the ELISA and enzyme inhibition assays, at appropriate times during the clinical trials. Until the specific test for IgE is appropriately designed and validated, serum samples will be collected and banked for future analysis. The protocol for assay methods and the validation plan for the antigen-specific IgE assay will be submitted to CBER by December 30, 2002. The complete validation data will be available December 30, 2003, and a final report submitted to CBER by March 31, 2004.

You have committed to collect and analyze data, as part of ongoing and future protocols, to further characterize the incidence of immune responses utilizing the assays specified in commitments 4-6 and to evaluate the pharmacodynamic and clinical consequences of such immune responses. In addition, analyses of the relationship of development of IgE or IgG antibodies to development of allergic reactions will be conducted within and across studies. All serum samples collected for immunogenicity testing will be sent to Sanofi-Synthelabo, Inc., who will be responsible for appropriately tracking, storing, and aliquoting a sufficient number and volume of sera for all three assays. When qualified assays have been developed and determined to be acceptable to CBER, the assays will be used to test the stored serum samples and all samples subsequently collected for immunogenicity testing. The specific studies are follows:

7. To include in all corporately-sponsored, ongoing or future studies, a systematic approach for collection of serum samples at baseline in all patients and, in those patients who experience an allergic reaction, additional serum samples will be collected within 48 hours of the reaction, at three months, at six months, and every six months thereafter, until the immunogenicity assays described above are validated. Once validated assays are available, only patients with persistent immune responses at six months will have serum collected every six months for each assay, until the results of all assays are negative. A proposal for the following will be developed: systematic collection and analysis of plasma uric acid levels in patients with antibody responses including allergic reactions; collection and reporting of adverse events; analysis of the pharmacodynamic effects of antibody responses; and, analysis of the correlation between allergic reactions and antibody assay results. Copies of revised protocols containing these modifications will be submitted by August 31, 2002 for all on-going studies.

You have also committed to incorporate a plan in two studies (described in items 8 and 9) to collect and analyze data that will further characterize the incidence, type and duration of immune responses in all patients enrolled in those studies, [i.e., in those with and without allergic reactions (All-Patient Schedule)]. Both studies will also include a plan for collection and analysis of data to characterize the pharmacodynamic effects and clinical consequences of the various types of immune responses. In both studies, serum will be collected at baseline, between 7 to 14 days, at five weeks, three months and six months after Rasburicase dosing, then every six months thereafter until the immunogenicity assays described above are validated. These two studies will utilize the assays specified in commitments 4-6. Once validated assays are available, only patients with persistent immune responses at six months will have serum collected every six months for each assay, until the results of all assays are negative. All patients with an allergic reaction will have additional serum collected within 48 hours after the allergic reactions as described in commitment 7 above. The specific studies are as follows:

8. To conduct a study to assess the safety and efficacy of repetitive treatment with Rasburicase. This study will enroll at least 100 uricolytic therapy-naive patients and 50 patients with prior exposure to uricolytic therapy. Antibody therapies directed against B-cells, including but not limited to rituximab, may not be administered to patients on study or within the 12-month period prior to study entry because they will confound the ability to assess immune responses. Data will be collected on concurrent antineoplastic therapy, on the most recent prior chemotherapy regimen, and on uric acid levels immediately prior to and during Rasburicase therapy. Immunogenicity studies will use the All-Patient Schedule described above. Plasma uric acid levels will be assessed at pre-specified time points in all patients and should be sufficient to assess maintenance of uric acid over various time points throughout Rasburicase treatment. Maintenance of uric acid levels will be as defined in the package insert. The protocol will include a detailed description of the analyses to characterize the following:

    a. the incidence, duration, and type of immune responses (i.e., IgG, IgE, neutralizing);

    b. clinical toxicity associated with an immune response;

    c. maintenance of uric acid levels at 4, 24, 48, 72 and 96 hours after first dose of Rasburicase;

    d. impact of immune response on maintenance of uric acid levels, i.e., pharmacodynamic impact; and,

    e. effect of prior uricolytic treatment on ability to maintain uric acid levels below the upper limit of normal and on immune response.

The draft protocol will be submitted by August 31, 2002, and a final protocol will be submitted by November 30, 2002. The study will be completed by December 31, 2005. The final study report, will include an assessment of the binding (IgG), neutralizing antibody, and IgE profile in naive and retreated subjects, the impact of immunogenicity on safety and efficacy, and the safety and efficacy of retreatment with Rasburicase. This report will be completed and submitted by September 30, 2006.

9. To conduct a study designed to assess the comparative safety and efficacy of the approved dose and schedule of Rasburicase with a regimen of sequential Rasburicase and allopurinol. This study will be conducted in adults and will enroll a sufficient number of subjects to randomize at least 60 patients (approximately 30 per treatment arm), following a short induction course of Rasburicase (two days treatment). The objectives of this trial will include a comparison of the adequacy of control of plasma uric acid concentration and comparison of the toxicity profile for the two regimens, including the comparability of the immunogenicity profile of Rasburicase in the two regimens. This study will use the all-patient schedule to assess immunogenicity. Plasma uric acid levels will be assessed at pre-specified time points in all patients and should be sufficient to assess maintenance of uric acid over various time points throughout Rasburicase treatment. Maintenance of uric acid levels will be as defined in the package insert. The protocol will include a detailed description of the analyses to characterize the following in each arm and a comparison between arms;

   a. the incidence, duration, and type of immune responses (i.e., IgG, IgE, neutralizing);

   b. clinical toxicity associated with an immune response;

   c. maintenance of uric acid levels at 4, 24, 48, 72 and 96 hours after first dose of Rasburicase; and,

   d. impact of immune response on maintenance of uric acid levels, i.e., pharmacodynamic impact. The protocol will include a detailed description of all analyses intended to assess these objectives.

   A draft protocol will be submitted by August 31, 2002, and the final protocol will be submitted by November 30, 2002. Accrual to the study will be completed by September 30, 2004. The final study report will include an assessment of the binding (IgG), neutralizing antibody, and IgE immunogenicity profile, the impact of immunogenicity on safety and efficacy, and the analysis of the comparable safety and efficacy of the sequential regimen to the approved regimen. The final study report will be completed and submitted by June 30, 2005.

10. For both expanded access studies ——— and ———, Sanofi-Synthelabo agrees to submit a draft publication, protocol, blank case report forms, case report forms for all serious adverse events and deaths within 30 days of dosing, and an electronic database that includes demography, dosing and safety information to CBER by September 30, 2003. Sanofi-Synthelabo agrees to attempt to collect additional information on volume and rate of administration of Rasburicase in patients three months of age or younger.

The protocols described in items 7, 8, and 9 above may be submitted for review under the Special Protocol Assessment procedure. Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" available at http://www.fda.gov/cber/gdlns/protocol.htm and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)** in bolded block letters at the top of your cover letter.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted in accordance with 21 CFR 600.81. Postmarketing adverse experience reports and distribution reports should be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. All adverse experience reports should be prominently identified according to 21 CFR 600.80.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit three draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 356h or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 356h or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Steven A. Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research